REMARKS

Claims 13-28, 31-38, 40-50 and 52-70 are pending in the application. Claims 1-12, 29, 30, 39 and 51 have been withdrawn from consideration. Claims 13, 31, 38, 40 47-50, 52, 58, 63, 66, and 67 are amended herein, claims 23 and 70 are canceled, and new claims 71-83 are added. No new matter is added to the claims by the amendments.

Claims 38, 47-50 and 58-62 have been objected to as depending from both elected and non-elected claims. The examiner requested that these claims be amended such that they are dependent only on the base claims of the elected invention. Applicants respectfully submit that this objection has been obviated by the amendments herein to claims 38 and 58.

Claims 13-22, 24-28, 31-38, 40-50 and 52-70 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the invention at the time the application was filed. The examiner acknowledged that the specification provides sufficient written description of liposomal vector carriers having a mean diameter of less than about 100 nm, wherein the vector carrier comprises a liposomal complex composed of a cell-targeting ligand bound to a cationic lipid, a therapeutic agent and a neutral or helper lipid but asserted that the specification does not provide sufficient written description

of a representative number of other species of liposomal carriers having a mean diameter of less than about 100 nm.

Applicants respectfully submit that this rejection has been obviated by the amendments above to the independent claims which make explicit that the liposomes are cationic liposomes comprising a cationic lipid and a neutral or helper lipid.

Claims 13-22, 24-28, 31-38, 40-50 and 52-70 have been rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification does not enable the claims. The examiner acknowledged that the specification is enabling for liposomal vector carriers having a mean diameter of less than about 100 nm and comprising a liposomal complex composed of a ligand bound to a cationic lipid which is DOTAP/DOPE, DDAB/DOPE, and a plasmid DNA encoding a wild type p53 tumor suppressor protein, a method of delivering a nucleic acid encoding a protein to a mammal by administering such a liposomal vector carrier, and a method of ameliorating a tumor in a mammal by administering such a liposomal vector carrier. He asserted, however, that the specification does not enable other embodiments as broadly claimed within the pending claims. The examiner asserted that the claims are not enabled for any cationic lipid/helper lipid/DNA complex other than DDAB/DOPE/plasmid DNA and DOTAP/DOPE/plasmid DNA. He asserted that there was no evidence that the procedures used to make these two specific complexes could be used to make complexes employing other lipids or other types of therapeutic agents. He quoted from a 1997 reference by Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 14(2):173-206, in which the authors stated that cationic liposomes cannot efficiently condense DNA and that the complexation usually results in the formation of spaghetti-

like structures, often accompanied by the generation of vectors of relatively large size with a tendency to aggregate. This rejection is traversed.

Applicants respectfully submit that they have fully enabled the claims of their application. Applicants have provided detailed information on the composition of the liposomes, the ratio of cationic to neutral lipids, the ratio of liposomes to ligand and the ratio of liposome and ligand to DNA. They have provided detailed information on how to make the complexes. They have provided seven specific examples of liposomes (identified as A-E and G-H; see Example 17) and have prepared complexes comprising several highly different types of molecules -- several different nucleic acids, antisense DNA and a virus -- as the therapeutic or diagnostic molecule of interest. They have provided experimental data showing the transfection efficiencies of complexes comprising each of the seven liposomes with a variety of different cell lines and showing the effectiveness of several of the complexes in treating human cancer xenografts in mice. Subsequent to filing this application they have published additional data showing the effectiveness of liposome complexes comprising ligands other than the two exemplified in the application in targeting human tumor xenografts. See, for example, Xu, L., et al., *Molecular Medicine* 7(10):723-734 (2001),and Xu, L., et al., *Molecular Cancer Therapeutics* 1:337-346 (2002), copies of which are enclosed. Also enclosed is a copy of Rait, A. et al., *Molecular Medicine* 8(8):475-486 (2002), which describes the tumor targeting of liposome complexes comprising antisense HER-2 to human breast cancer xenografts. The Applicants have, in short, provided a

large and highly significant amount of experimental data which clearly illustrate their invention.

The examiner's reliance on the reference by Lee et al. is misplaced. This is an old reference, and the field has moved forward significantly since it was published -- in large measure due to the work of the Applicants. Example 24 of their application shows that when cationic and neutral lipids, ligand and DNA are mixed in the order given and at the ratios set forth in the application, the DNA will condense efficiently without the need for other condensation reagents. Example 24 illustrates that their invention produces complexes that are not spaghetti-like and that have a mean diameter of less than 100 nm. This also is illustrated in a paper by the inventors, Xu, L., et al., *Human Gene Therapy* 13:469-481 (2002), a copy of which is enclosed, which provides illustrations of cryo-EM analysis of liposome complexes of the present invention, showing the complexes clearly to be spherical in shape, with the ligand coating protruding from the liposome surface and the DNA fully encapsulated within the liposome.

In view of the data presented, Applicants respectfully submit that they have fully enabled the present invention.

The examiner further asserted that with regard to the claiming of "any method of gene therapy and/or the use of any liposomal carrier having the claimed diameter as a vector gene therapy, the state of the prior art with respect to non-viral gene therapy remains reasonably unpredictable." He cited the Lee et al. paper again, which stated that "it is difficult to predict the performance of a specific cationic liposome formulation based simply on the cationic lipid structure and/or the lipid

composition" and that the gene transfer property of a vector was determined by a variety of factors, including particle size, lipid composition, lipid/DNA ratio, formulation procedure, DNA concentration, strength and tissue specificity of the promoter and enhancer elements, and delivery variables for *in vitro* and *in vivo* delivery.

Applicants respectfully submit that the data they have provided clearly illustrate that the complexes of their invention can effectively target cells *in vivo*. As noted above, they have provided within their application and the publications enclosed herewith a number of illustrations that complexes of their invention target human xenografts in mice and are effective in either reducing tumor size or eliminating the tumor completely. See, for example, Xu, L., et al., Molecular Medicine 7(10):723-734 (2001); Xu, L., et al., Molecular Center Therapeutics 1:337-346 (2002); Rait, A. et al., Molecular Medicine 8:475-486 (2002); Xu, L., et al., Human Gene Therapy, 10:2941-2952 (1999); Xu, L., et al., Tumor Targeting, 1(4):92-104 (1999); Xu, L., et al., Human Gene Therapy, 1(13):469-481 (2002) enclosed. They also show that the complexes target both primary tumors and metastatic tumors.

The examiner also cited a 1996 paper by Kao et al., *Cancer Gene Therapy* 3(4):250-256, whish states that "with one or two notable exceptions, to date there are no successful examples of satisfactory transfection after systemic administration of liposomes and no examples exist of successful transfections *in vivo* using targeted liposomal DNA systemically." Kao et al. further stated that they expected that "considerable formulation development, directed at increasing the circulation times of

liposomal DNA will be needed before targeted DNA delivery to cancer cells will be realized *in vivo*."

Although the examiner has chosen to interpret these comments as illustrating that gene therapy is not possible, Applicants submit that a more reasonable interpretation is that successful gene therapy is possible (the author notes that as of 1996 there had been a couple of successes) and that the authors believe that gene therapy will become more generally achievable ("development... will be needed *before* targeted DNA delivery to cancer cells will be realized *in vivo*" (emphasis added)). The current inventors' work illustrates that that optimism was well-founded. They have provided that needed development. They provide numerous examples in their application (including examples 6, 10, 11, 12, 16 and 19-22) which demonstrate that the method of their invention does achieve targeted delivery of DNA to cancer cells.

The examiner concludes this rejection by stating that the specification fails to provide sufficient guidance or evidence "to overcome the doubts expressed by the art of record." He further avers that the simple inhibition of a tumor in a murine model through the administration of either of two specific liposome complexes "does not appear to be correlated to any therapeutic effect by using any other therapeutic DNA in cancer gene therapy in any cancer patient, let alone any other gene therapy for treating any disease or disorder in any animal."

Applicants respectfully submit that the examiner has failed to fully consider all of the data presented in the present application. Applicants have shown the beneficial therapeutic effects obtained by the present invention not just with p53 as the therapeutic agent, but also with anti-sense HER-2

oligonucleotides. See Example 21 of the application, which describes the uptake of liposome complexes comprising the anti-sense Her-2 oligos by tumor cells and their *in vivo* efficacy following systemic administration.

In addition, the application contains examples showing the delivery of DNA encoding β-galactosidase (see Examples 3, 5, 6 and 17) and luciferase (see Examples 4 and 17) to cells. Although β-galactosidase and luciferase are not therapeutic molecules, these examples still provide evidence that the delivery system does effectively deliver a variety of types of molecules to target cells.

The examiner quotes a 1997 reference by Verma and Somia that "'the Achilles heel of gene therapy is gene delivery.'" Regardless of whether this was true in 1997, Applicants respectfully submit that through their work, described and claimed in this application, they have found a useful and reproducible way to deliver genes to target cells of interest. The examples in their application clearly show that tumor specific targeting is achieved following systemic administration of their liposomal complexes. See Examples 3, 5, 6 and 17.

The examiner also relies upon the Verma and Somia reference as indicating that the factors involved in achieving successful gene therapy include the nature of the disease, the nature of the DNA and/or target tissue, the delivery system and/or the amounts of DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo*. Applicants have shown in their examples *in vivo* targeting and efficacy in a number of types of cancer -- head and neck cancer, prostate cancer, breast cancer and pancreatic cancer. They further show *in vitro* targeting and

efficacy in an even wider array of cancers (see tables 1-3 of Example 17).

The examiner further cites a 1998 paper by Anderson in *Nature* and characterizes the paper as "teaching" that the reason for low efficiency of gene transfer and expression in human patients is that there remains a lack of basic understanding of how vectors should be constructed and what regulatory sequences are appropriate. This is Anderson's *opinion*, not fact, and Applicants have shown that they achieve high expression of different molecules of interest in target cells. See Examples 3-7 and 17 of the application. Further, the focus of Anderson's paper is viral-based delivery systems and the problems involved with viral-based gene delivery; non-viral vectors are given a single small paragraph of very general discussion, the thrust of which is that non-viral gene delivery systems (such as that of the present invention) will be the preferred choice.

The examiner further cited a paper by Filion, *International J. Pharmaceutics* 162:159-170 (1996), from which the examiner quoted a statement that the use of cationic liposomes "to target DNA to the gastrointestinal tract is inappropriate" as such liposomes are highly toxic to mice following the administration of a single dose.

Applicants respectfully point out to the examiner that a key benefit of their invention is that the complexes target specific cells of interest. In the case of cancer treatment, the complexes target cancer cells very specifically and do not target normal cell tissue (e.g., the gastrointestinal tract). This is illustrated by the enclosed page of color figures, the second set of which show the results of *in vivo* liposome/folate-mediated

systemic transfection of the β-galactosidase reporter gene in nude mouse DU145 xenografts, 48 hours post-injection. The β-Gal-expressing cells stain blue. As is clearly seen in the figure, Panel A, which shows the xenograft tumor, is significantly blue, showing the strong presence of the β-Gal. Panels C and D are images of normal lung tissue and normal large intestine tissue from the injected mouse carrying the xenograft tumor; it is apparent from both that the complex targets the tumor tissue and not the normal tissue. Panel B represents a control. Animals which have been administered complexes of this invention have not shown toxic effects.

The examiner concluded the rejection of the claims under §112 by asserting that it is not apparent how one skilled in the art could determine which of the disclosed DNA complexes could be used to generate a therapeutic effect in a method of gene therapy, nor how one could extrapolate from the teachings of the specification to *in vivo* delivery and/or expression methods. He asserted that because the *in vivo* data presented in the application were obtained from mice, the application did not enable the administration to humans, as the mouse is not an effective model for cancer treatment in humans.

Applicants respectfully submit that the examiner's conclusion regarding the suitability of the mouse as a model for human treatment is over-reaching and, therefore, inaccurate. Contrary to the examiner's assertions, the nude mouse is an accepted model in the development of human cancer therapy. The examiner appears to have overlooked that although the *in vivo* experiments were carried out in mice, the mice were ones in which xenografts, i.e., human tumors, had been induced. The use of xenograft-induced mice

is, in fact, the standard model in the field of cancer treatment. Applicants respectfully direct the examiner's attention to the website for the National Cancer Institute, an entire section of which focuses on mouse models. The NCI has a collaborative program, the NCI Mouse Models of Human Cancers Consortium, (MMHCC), and sponsors a variety of other projects to "develop, analyze and apply mouse cancer models." See the first page of the "e-mouse" portion of the NCI website, a copy of which is attached. Also attached is the first page of the "Mouse Models" subsection of that portion of the site.

The examples provided in the application present the use of complexes of the invention against numerous types of cancer cells (Examples 17 and 18) *in vitro* and breast, prostate, head and neck and pancreatic cancer *in vivo*. These represent a broad spectrum of human cancers and in each instance a human cancer cell line and xenograft tumors were used. Applicant have showed effective activity with more than one composition, indeed, they have presented 25 illustrations of how to make and use the invention. They have given specific ratios and detailed descriptions of how to make seven different complexes, all of which were tested in human cancer cells at least *in vitro*.

Enclosed with this Amendment is a declaration by one of the Applicants, Dr. Esther Chang. Dr. Chang notes that the efficacy of the work she and her co-inventors have done are demonstrated not only by the data presented in their peer-reviewed publications demonstrating *in vivo* systemic anti-cancer efficacy in a variety of different tumor models, but by the fact that their work has been recognized nationally and internationally. Their work has been reproduced within the Developmental Therapeutics Division of

the National Cancer Institute (NCI), and the NCI is collaborating with them to move their delivery system into clinical trials against cancer. They also have presented their work by invitation at over twenty national and international meetings, including the 6th US-Japan Cellular and Gene Therapy Conference in February, 2003, at the invitation of the U.S. FDA. This is clear evidence that their peers and colleagues see their work as credible and as providing an effective methodology for the systemic, targeted delivery of therapeutic agents for cancer therapy.

Claims 13, 16, 17, 19-21 and 24-25 have been rejected under 35 U.S.C. § 102(b) as anticipated by Wang et al., *Biochemistry* 92:3318-3312 (1995). The examiner asserted that Wang et al. teach a liposomal carrier composed of folate-PEG-DOPE which encapsulates antisense oligos against EGF receptor and that these liposomes can deliver sufficient antisense against the EGF receptor into KB cells to eliminate EGF receptor expression, alter cell morphology and halt cell growth. The examiner further asserted that the paper teaches that the liposomal complexes can be formulated by a size reduction procedure of extrusion through a 100 nm polycarbonate membrane and that this necessarily indicates that the mean diameter of the liposomes after extrusion necessarily is less than 100 nm. This rejection is traversed.

As the examiner correctly noted, the complexes disclosed by Wang et al. require that the folate ligand be bound to the liposome through a PEG linker. No such linker is required or present in the complexes of the present invention. The pending independent claims have been amended to make explicit what is clear from the specification-in the complexes of the present invention, the ligand is bound directly to the liposomes. Support

for this amendment can be found, *inter alia*, in Example 2, which details the formation of liposome-ligand complexes. As the complexes claimed in this application do not contain a necessary element of the complexes of the cited reference, the reference does not anticipate the claimed invention.

Claims 13-17, 19-20, 22-28, 31, 33-38, 40-48 and 63-70 have been rejected under 35 U.S.C. § 102(e) as anticipated by, or under 35 U.S.C. § 103(a) as rendered obvious in view of, U.S. Patent 6,077,834, issued to Cheng. The examiner asserted that the '834 patent teaches an identical liposomal complex to that claimed in the application, consisting essentially of a liposomal complex composed of a cell-targeting ligand bound to a liposome comprising a cationic lipid and a neutral lipid, and a therapeutic nucleic acid encoding a therapeutic protein. The examiner further asserted that the production process of the '834 patent is embraced by the claimed process, and, therefore, it necessarily would flow from the teaching of the patent that the complexes after mixing and incubation must exhibit a mean diameter of less than 100 nm. The examiner averred that the '834 patent teaches both the size and shape limitations of the liposomal complexes, particularly in the absence of evidence to the contrary. This rejection is traversed.

All of the pending claims of the present application contain the limitation that the complexes of ligand, cationic liposome and therapeutic or diagnostic agent which are the focus of the invention have a mean diameter of less than about 100 nm. As Applicants teach on page 19 of their application, this small size and regular shape is important for the complexes to be resistant to serum and be able to pass through blood vessel walls and into

target tissue. In the Office Action, the examiner asserted that it necessarily would flow from the teachings of the '834 patent that the complexes produced therein would have the same size and shape limitations of the complexes claimed by applicants. This assumption by the examiner is not correct.

The complexes which are the focus of the '834 patent, and the ones which are the subject of the examples, are complexes made using commercially available liposomes, lipofectin, a formulation of DOTMA and DOPE, and lipofectace, a formulation of DDAB and DOPE. These formulations are said to be "preferred" (column 3, lines 42-47). In each of the Examples of the patent, complexes are made using lipofectin and transferrin.

The enclosed Declaration by Dr. Esther Chang addresses the '834 patent. As Dr. Chang explains in the declaration, the complex taught in Example 1, col. 11, lines 14-28, using the preferred ratios of 1.5 µg DNA/3 µg lipofectin/32 µg transferrin (Tf), with the DNA and Tf in HBS and allowing 15 minutes between additions, was prepared several times under her direction. Each of the resulting products had a fine precipitate. The cumulative mean size average of the resulting complexes from several measurements was found to vary from 207.8 to 376.8 nm, well above the mean diameter of less than 100nm required by the claims of this application. In addition, the complexes made following the teachings of the '834 patent had a polydispersity which varied from 0.453 - 0.895, which indicates an unacceptably high level of heterogeneity in particle size. By intensity, the size varied from 7.6 to 8810.4 nm. It is well-known to persons of skill in the art that a size in the range of 7-8 nm represents

unincorporated DNA. The complexes thus were quite different in size from the complexes claimed in the present application.

Not only was the size very different from that of the presently claimed complexes, the Zeta potential of the complexes made following the teachings of Example 1 of the '834 patent varied from -33.2 to -32.3. This indicates that the complex had a large net negative charge and thus is anionic, not cationic as indicated in the '834 patent.

Furthermore, the '834 patent provides, in Figure 4, an illustration of the desired complexes of the invention. Two different complexes are shown, at the bottom left-hand and bottom right-hand sides of the drawing. The favored complexes, as described within the specification, are those at the lower right hand side of the drawing (labeled "B"). Both of the illustrated structures are elongated, "spaghetti-like" structures which are quite different from the complexes of the present invention. In neither of these structures is the DNA encapsulated within the liposomes. Indeed, the '834 patent does not teach that the DNA is encapsulated within the liposomes; the patent refers to DNA as "binding to" the lipofectin and transferrin (column 7, lines 6-7). In contrast, as described in Example 24 of the present application, in the complexes of the present invention, the DNA or other agent of interest is encapsulated within the liposomes. Results comparable to those described in Example 24, are illustrated, as noted above, in the enclosed 2002 publication by the inventors which provides electron microscopy images of complexes of the present invention, which are shown to be essentially spherical, with DNA condensed inside the liposome and the ligand bonded to the outside of the liposome.

These differences in size and shape and, most importantly, charge, are very significant and greatly affect the usefulness of the complex to deliver therapeutic or diagnostic agents to target cells *in vivo*. The '834 patent does not provide any *in vivo* data, and to the best that the Applicants have been able to determine, the inventor has not subsequently published any papers showing that the complexes made as in the Examples of the '834 patent can be administered *in vivo* with beneficial results. This is not surprising, given that the method taught in the examples produced a complex that is anionic, rather than cationic. In contrast, the small, spherical cationic structures of the present invention have been shown to have extremely good *in vivo* targeting specificity and activity.

Thus, contrary to the examiner's assertion, the '834 patent does not teach ligand-liposome-DNA complexes having a mean diameter of less than 100 nm. The patent does not recognize a benefit to particles of this size or suggest that the complexes should have a mean diameter of less than 100 nm. Further, by following the specific teachings in the '834 Examples, one does not obtain complexes having the mean diameter required by the claims of this application. The '834 patent, therefore, does not anticipate the presently claimed invention. Further, because the patent also does not even suggest such complexes or provide specific guidance toward making such complexes, the patent does not render such complexes, or their administration, obvious.

Claims 13-17, 19-20, 22-28, 31, 33-38, 40-48 and 63-70 of the application have been rejected under 35 U.S.C. §102(b) as anticipated by, or under 35 U.S.C. § 103(a) as obvious in view of,

Cheng et al., *Human Gene Therapy* 7:275-282 (1996). This rejection is traversed.

The Materials and Methods portion of the paper by Cheng et al. is essentially the same as Example 1 of the '834 patent discussed above. The discussion of the shortcomings of the patent and the differences between the complexes formed in Example 1 and the complexes of the present invention is equally applicable to this reference. The teachings of this reference thus neither anticipate nor render obvious the present invention.

Claims 13-17, 19-21, 23-28, 31, 33-38, 40-48 and 63-70 have been rejected under 35 U.S.C. § 103(a) as obvious over the '834 patent, taken in combination with Lee et al., *J. Biological Chemistry* 271(14):8481-8487 (1996) and Gao et al., *Biochemistry* 35: 1027-1036 (1996), and further in view of U.S. Patent 6,028,066, issued to Unger et al. (hereinafter referred to as the '066 patent). The examiner stated that it would have been obvious to have used polylysine to potentiate a cationic liposome-mediated delivery of DNA to a cell in a mammal, such as the liposomal/targeting ligand/DNA complexes disclosed in the primary reference because both Lee et al. and Gao et al. teach that polylysine helps to potentiate cationic liposome-mediated delivery of any DNA to a cell in a mammal. The examiner further asserted that it would have been obvious to use folate as a ligand because Lee teaches that folate-conjugated liposomes have been shown to be specifically taken up by cultured receptor bearing tumor cells. The examiner further averred that it would have been obvious to use shaking techniques because Unger et al. teaches that it is well known in the art of making liposomal formulations to employ shaking techniques and/or vortexing to make or formulate liposomal

vesicles containing stabilizing materials at a preferred size range. This rejection is traversed.

The shortcomings of the '834 patent are discussed above, and that discussion is equally applicable to the present rejection. The secondary and tertiary references cited by the examiner do not compensate for the deficiencies of the primary reference. The examiner's reliance on the Lee et al. and Gao et al. papers and specifically, his statement regarding the use of polylysine to help potentiate cationic liposome-mediated delivery, is not understood. Applicants do not teach or claim the use of polylysine or other condensing agent to bind to the therapeutic agent prior to contact it with lipids. In addition, Lee et al. focus on anionic, rather than cationic liposomes. There are significant differences between positively charged (cationic) and negatively charged (anionic) particles, as would be well-understood by persons of ordinary skill in the art. The authors state on page 8482 that their novel anionic DNA vector was more efficient and less cytotoxic than conventional cationic liposome vectors. There is no suggestion in the paper that the complexes could be made using cationic liposomes in place of the anionic liposomes.

Lee et al.'s use of folate also is different from Applicants'; Lee et al. require that folate be conjugated to PEG, a large hydrocarbon molecule. As already discussed above, Applicants do not conjugate or bind their ligand to PEG.

Finally, Lee et al. state on page 8487 of their paper that "[u]nlike cationic liposome complexes which usually undergo slow aggregation upon storage, our novel (anionic) vectors were small in size ...." Such a statement actually teaches away from the use

of cationic liposomes as a delivery vehicle and shows that the small cationic liposome complexes of the present invention represent an improvement over the state of the art and are not obvious.

The teachings of the Gao et al. paper also are not relevant to the present invention. Again, Applicants do not use a cationic polymer to condense DNA, and there is no mention of polylysine in their invention description or claims.

The combination of the teachings of this reference with those of Lee et al. and the '834 patent thus would not lead one to the cationic liposome complexes of the present invention.

The '066 patent also is not relevant to the present invention, and combining its teachings with those of the other cited references would not lead one to the presently claimed invention. The '066 patent focuses on novel prodrugs comprising fluorinated amphiphiles. Lipids can be used as stabilizing vehicles for the prodrugs. The patent does not focus on targeted gene delivery. The patent describes conventional methods of shaking and/or vortexing to make empty liposomes, not complexes of a ligand, cationic liposome and therapeutic or diagnostic agent.

Claims 13-28, 31-38, 40-50 and 52-70 have been rejected under 35 U.S.C. §103(a) as obvious over the '834 patent or the Cheng et al. paper, taken with U.S. Patent 6,069,134, issued to Roth, and the Wang et al. paper. The examiner stated that the primary references do not teach a method of killing tumor cells through a combination of radiation or chemotherapy and the systemic administration of a vector carrier encoding a wtp53 protein to a tumor bearing subject, but that the '134 patent teaches a method of killing tumor cells through the combination of radiation or

chemotherapy and the systemic administration of a liposomal vector carrier and wtp53. The examiner further averred that the Wang et al. paper teaches that folate-PEG-liposomes can deliver antisense against the EGF receptor into cells to eliminate EGF receptor expression and halt cell growth. The examiner concluded that the claimed invention as a whole was obvious. This rejection is traversed.

The deficiencies of the '834 patent and the Cheng et al. paper have been discussed above, and that discussion is equally applicable to the present rejection. The cited secondary references do not compensate for the shortcomings of the primary references. The '134 patent focuses on viral-mediated gene transfer, not liposome-mediated gene delivery. Although the patent indicates at column 8, lines 42-44 that liposome-mediated transfection is envisioned, the patent provides no information on how to prepare or use liposomes, and, in column 21, lines 40-46, the patent states that although other researchers have reported the formation of liposomes from certain lipids and amphophilic peptides, the present efficiency of gene integration "is very low. It is estimated that the gene of interest integrates into the genome of only one cell in 1,000 to 100,000." In other words, liposome-mediated transfection is ineffective. This reference thus does not teach or suggest the treatment of a tumor through the administration of a liposome carrying a therapeutic agent in combination with chemotherapy or radiation therapy. The deficiencies of the Wang et al. paper also have been discussed above. Wang et al. require the presence of a PEG linker between the ligand and the liposome. Such a linker is not a part of the present liposome complex. None of the cited references, taken

independently or in combination teach or suggest the liposome complexes of the present invention nor the administration of those complexes, alone or in combination with a conventional therapy, to treat tumors.

Claims 13-28, 31-38, 40-50 and 52-70 have been rejected under 35 U.S.C. § 103(a) as obvious over the '834 patent taken with Lee, Gao and Unger and further in view of the '134 patent. The references were applied as in the previous rejections. The examiner acknowledged that the first four of the cited references do not teach a method of killing tumor cells through the combination of radiation or chemotherapy and the systemic administration of an vector carrier encoding a wild type p53 protein to a tumor-bearing subject. He asserted, however, that the '134 patent does teach such a method and that it would have been obvious to have employed the delivery method and carrier disclosed in the '834 patent taken with the Lee, Gao and Unger references and to administer the carrier systemically in combination with a conventional therapy as taught in the '134 patent. This rejection is traversed.

Each of these references has been discussed above. Each of the references has significant shortcomings. The combination of references does not teach or suggest the present invention, a cationic liposome-ligand complex having a mean diameter of less than 100 nm, or its use as a therapeutic or diagnostic agent, as required by the present claims.

In view of the foregoing amendments and discussion, Applicants respectfully submit that their application is in condition for allowance.

Respectfully submitted,

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